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Optimal antibiotic use in the intensive care unit

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Abstract

Background Antibiotic resistance has emerged as one of the most important factors influencing the outcomes of patients with life-threatening infections in the ICU. The increasing prevalence of antibiotic-resistant infections globally highlights the importance of this issue for all intensivists.

Main body Antibiotic utilization in the ICU should be optimized to ensure that timely appropriate treatment is administered in a way that minimizes the subsequent emergence of antibiotic resistance. Antibiotic strategies have been developed to assist clinicians in achieving this important balance. Familiarity with local ICU pathogens and their antibiotic susceptibilities is at the forefront of optimizing ICU antibiotic practices. Moreover, timely antibiotic administration along with pharmacokinetic/pharmacodynamic (PK/PD) optimization, including ideal dosing and infusion duration, should be key components of all ICU antibiotic strategies. Microbiologic testing to include conventional pathogen identification and susceptibility testing as well as use of microbiologic rapid diagnostic tests can confirm the antibiotic regimen that is required to treat the causative pathogens while allowing de-escalation to occur if possible. Similarly, biomarkers such as procalcitonin can aid with avoiding unnecessary antibiotic use in the ICU and shortening their overall duration. ICUs should routinely employ formal programs for reviewing and optimizing antibiotic practices. These programs can include directed input from pharmacists and microbiologists during ICU rounds, the use of specialized order sets focusing on duration of treatment with stop as well as dosing optimization guidance, use of computerized decision support tools, incorporated protocols for the prevention of nosocomial infections, and the appropriate use of antibiotic prophylaxis regimens to include selective digestive decontamination (SDD). Tracking antibiotic practices in the ICU, as well as changing patterns of pathogens and antibiotic susceptibilities, mandate regular modification and updating of these practices over time. Antibiotic combination regimens can also be employed in some circumstances to increase the likelihood of treatment success with an appropriate initial regimen while also reducing the propensity for resistance emergence. Additionally artificial intelligence/machine learning (AI/ML) methods will increasingly serve to enhance antibiotic decision making in the future.

Conclusion Antibiotic optimization strategies in the ICU should routinely be employed by a multi-specialty group including intensivists, microbiologists, pharmacists, infectious disease specialists, and infection control practitioners.

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Regular review and updating of ICU antibiotic practices will help to safeguard their long-term use to optimize patient outcomes while minimizing resistance emergence.

Keywords Antibiotics, Intensive care unit, Resistance, De-escalation, Bacteria, Infections, Intensivists

Background

Antimicrobial resistance is a growing healthcare problem globally. The Centers for Disease Control and Prevention (CDC) 2019 Threats Report estimates that more than 2.8 million antibiotic-resistant infections occur each year, with More than 35,000 deaths resulting from antibiotic-resistant infections. Adding deaths from *Clostridiodes difficile* increases the US toll of these threats to More than 3 million infections and 48,000 deaths. Similar data regarding the threat of antibiotic-resistant infections has been generated by the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO). With these data in mind the aims of this review are to offer clinicians evidence-based guidance concerning the optimal use of antibiotics in the ICU. Optimizing ICU antibiotic practices should improve patient outcomes while minimizing the emergence of antibiotic resistance. The literature examined for this review came from a MEDLINE search focusing on the terms antibiotics, resistance, stewardship, intensive care, de-escalation, bacteria, and infection. The main issue under discussion is optimization of antibiotic utilization in the ICU setting.

Introduction

Antibiotics are commonly prescribed in the intensive care unit (ICU) setting (Table 1). The frequent use of antibiotics is largely driven by the high density of infections, often life-threatening infections, treated in ICUs. European Prevalence of Infection in Intensive Care (EPIC) III, an international point prevalence study of ICU infections, found that the proportion of patients with suspected or proven infection Ranged from 43% in Australasia to 60% in Asia and the Middle East [1]. EPIC III also showed that infection with specific antibiotic-resistant microorganisms was independently associated with a greater risk of hospital death [1]. Antibiotic exposure is known to promote the occurrence of healthcare-associated infections as well as the development of antibiotic resistance [2–5]. Moreover, critical illness alters patient antibiotic pharmacokinetic/pharmacodynamic (PK/PD) parameters and influences tissue drug levels at the infection site which impacts both the agents' efficacy and the propensity for resistance to emerge [6, 7]. Lastly, it has been repeatedly shown that there is overutilization of antibiotics in hospitalized patients including within ICUs [8, 9].

The high prevalence of infections in ICUs, and the need to treat such infections with antibiotics in the critically ill, warrants a critical appraisal of such therapy to optimize patient outcomes and minimize subsequent resistance emergence. The rapidly increasing body of literature focusing on antibiotic utilization in the ICU setting serves as the impetus for this sweeping review. We will not discuss antibiotic use outside of the ICU. However, we recognize that any prior antibiotic exposure may influence ICU patients by promoting patient colonization and infection with antibiotic resistant bacteria. Lastly, we hope to provide intensivists with a quality improvement framework for applying antibiotic stewardship (AS) practices in the ICU.

Initial empiric treatment and combination therapy

Given the high prevalence of sepsis and septic shock, intensivists frequently face the decision of initiating antibiotic therapy and selecting the appropriate regimen. Empiric therapy is started when an infection is suspected before microbiology results are available. Once the pathogen has been identified and susceptibility testing performed, the empiric regimen can be tailored to directed or definitive therapy. Concordant therapy refers to an antibiotic choice that is active against the isolated bacterium(a) based on in vitro susceptibility testing. In the ICU, recognizing an infectious process is crucial. No absolute constellation of signs and symptoms or tests can unequivocally diagnose sepsis, thus clinicians must rely on the available clinical information and decide under uncertainty if empiric antibiotics will be beneficial or harmful. Typical symptoms can suggest an infectious syndrome, but older patients with multiple comorbidities often present ambiguously, with a wider differential diagnosis and higher mortality absent appropriate treatment. Up to a third of patients with presumed sepsis may ultimately have a sepsis mimic and potentially experience harm from broad-spectrum antibiotics [10–12]. Critically ill patients have higher sepsis prevalence than non-ICU patients, therefore increasing the pretest probability of life-threatening infection.

The Surviving Sepsis Campaign and the Centers for Medicare and Medicaid Services (CMS) SEP-1 measures recommend immediate antibiotics—typically broad spectrum with MRSA and pseudomonal coverage — within 1 to 3 hours of sepsis recognition [13, 14]. Kumar et al described that each hour of delay in starting antibiotics led to a 7.6% decrease in survival for patients with septic shock [15]. Other studies, examining timely antibiotic administration alone or as part of a sepsis care bundle, supported these findings [16–20], with the greatest

benefit of early antibiotic initiation in patients with septic shock. Seymour et al.'s study of 50,000 patients treated for sepsis found that the 7% increased hourly risk of death was not present in those not requiring vasopressors [16]. This differentiation led IDSA to caution against blanket recommendations for Rapid antibiotics in all sepsis cases, favoring a Rapid evaluation within the first 3–5 hours [21, 22]. This way, uninfected patients may be protected from the side effects of broad-spectrum antibiotics. Even in critically ill patients suspected of having a hospital-acquired infection, too rapid initiation of antibiotics in the absence of shock can result in adverse consequences, including higher mortality [23].

Once infection probability warrants antibiotic initiation, clinicians must decide on the spectrum, hoping empiric choices will be concordant with culture results. This decision is complicated by increasing rates of resistant bacteria, such as MRSA, VRE, resistant Enterobacterales, *P. aeruginosa*, and *Acinetobacter* spp., especially in the ICU. Many retrospective studies have emphasized the life-saving effect of concordant antibiotics in serious infections (even in the absence of sepsis) [24–27], and antimicrobial resistance is linked to discordant antibiotics, affecting mortality. Adjusting for prevalence Rates among culture-positive severe sepsis and septic shock cases, our group found that 38 patients needed coverage for MRSA and *P. aeruginosa* to save one life [28].

Choosing an empiric regimen involves considering the infection site, likely bacteria, and estimating antimicrobial resistance based on patient characteristics and local epidemiology. Risk factors such as known colonization and exposure to the healthcare system—particularly prior antibiotic administration and residing in long-term acute care facilities—have been consistently associated with AROs. Colonization with resistant GNB, such as ESBL and carbapenem-resistant Enterobacterales, is rising even among community dwellers and ICU admission is a risk factor for invasive infections in colonized patients [29, 30]. Local resistance rates, often summarized in institution-specific antibiograms, determine the likelihood of resistant GNB and may even surpass patient comorbidities [31]. Prevalence rates extracted from culture-positive cases may overestimate ARO probability and not assist with sepsis uncertainty. Clinicians tend to overestimate the likelihood of resistant bacteria, especially in community-onset sepsis, leading to overly broad antibiotics, increasing antibiotic resistance risk and mortality [32, 33].

A new, large retrospective study by Baghdadi et al used Win Ratio to compare mortality, readmission and adverse events between early anti-GNB antibiotics and delayed - patients started on narrow spectrum and later broadened [34]. While most analyses favored the delayed group, patients with septic shock benefitted, albeit not statistically significant, by early broad-spectrum antibiotics. This study reflects real life overuse of antibiotics but does not diminish the real benefit of early antibiotic treatment in true serious infections. Newer prediction tools using machine-learning try to predict resistance especially in GNB infections [35–41]. The focus has shifted from labeling patients at risk for resistant microbes to identifying true negatives that can safely be administered narrow-spectrum antibiotics. Unfortunately, most tools are developed on culture-positive sepsis and their predictive performance greatly increases after certain microbes are identified, but this decreases their usability in guiding empiric choices [35, 38, 41–44]. Machine-learning-assisted antibiotic selection has shown modest to moderate improvement over physician performance in community and hospitalized patients, including critically ill patients [35, 44–46]. An analysis of 8,342 emergency department infections showed that personalized antibiograms provided similar coverage while eliminating unnecessary MRSA coverage in 69% of cases [35].

As machine learning tools become prevalent, they must incorporate culture-negative cases and demonstrate generalizability, given the local resistance rates' impact on model performance [31]. A significant step forward in selecting regimens that cover the current infections while minimizing future resistance will be combining whole-genome sequencing of pre- and post-treatment bacterial isolates with machine learning [47]. Critically ill patients will benefit greatly from similar approaches given the significant risk of colonization and subsequent invasive infections with AROs.

Combination therapy with a beta-lactam and an aminoglycoside might also decrease the emergence of resistant isolates during and post-treatment in patients with severe sepsis and septic shock [48]. Older trials using dated thrice-daily dosing regimens focused on initial isolate resistance and did not show a benefit [49]. Combination therapy was initially considered a strategy to increase pathogen coverage in the face of rising resistance rates, but prospective trials and meta-analyses have not supported improved survival and indicated additional nephrotoxicity [50, 51]. Therefore, we would only recommend the use of combination antibiotic therapy in several specific circumstances. First, as empiric coverage in life-threatening infections where highly resistant GNB infection is suspected and combination therapy is thought to provide a greater likelihood of appropriate initial coverage until susceptibilities are available (e.g., aztreonam and ceftazidime-avibactam for suspected MBL infection). Second, for specific infections where combination antibiotic therapy is warranted to improve patient outcomes and provide treatment of mixed infections or infections associated with toxin production (e.g., endocarditis, necrotizing fasciitis).

Table 1 Commonly utilized antibiotics in the ICU*

Antibiotic	Dosing	Clearance	Notes
Gram Positive Antibiotics			
Vancomycin	15-20 mg/kg IV q8-12 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Check vancomycin trough levels or AUC/MIC, dose adjustments may be necessary. Goal trough is typically 15-20 mg/L. Goal AUC/MIC is 400-600. Continuous infusions may be considered in patients who cannot achieve the AUC target with intermittent infusions.
Linezolid	600 mg IV or PO q12 hr	No dosage adjustments necessary for renal or hepatic dysfunction.	Weak MAOI; risk of serotonin syndrome when used with concomitant serotonergic drugs. May cause myelosuppression and peripheral and optic neuropathies, and lactic acidosis with prolonged use (typically >2 weeks). Considerable interindividual variability can occur with "standard dosing". TDM may be used when available.
Ceftaroline	600 mg IV q12 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	In addition to MRSA activity, has activity similar to typical 3rd generation cephalosporins (e.g., ceftriaxone).
Daptomycin	4-10 mg/kg q24 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Inactivated by pulmonary surfactant. Not appropriate for treatment of pneumonia. May cause myopathies, so CK should be monitored at baseline and at least weekly. May also cause eosinophilic pneumonia with prolonged use.
Gram Negative Antibiotics#			
Ceftriaxone	1-2 g IV q24 hr	Dosing adjustments not necessary for renal or hepatic dysfunction, dose needs to be increased to q12 hr in CNS infections	Extensive activity against typical gram-negative bacteria (E coli, Klebsiella, Proteus, and Salmonella) with activity against gram positive bacteria like Streptococcus and Staphylococcus. No coverage of Pseudomonas.
Ampicillin-sulbactam	3 g IV q 6 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Has activity against certain gram negative Enterobacterales (E coli, Klebsiella), excellent anaerobic coverage, and gram-positive coverage such as Streptococcus and Enterococcus faecalis. No Pseudomonas coverage. Does have coverage against Acinetobacter (sulbactam component only).
Cefepime	2 g IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Commonly used agent for empiric therapy in septic shock, broad Gram-negative coverage including Enterobacterales, and Pseudomonas. Active against AmpC beta-lactamases. No anaerobic coverage. May cause neurotoxicity such as encephalopathy and seizures.
Ceftobiprole	667 mg IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Extensive activity against typical gram-negative bacteria (E coli, Klebsiella, Proteus, and Salmonella) with activity against gram positive bacteria like Streptococcus and Staphylococcus (including MRSA). Also has some coverage against Pseudomonas.
Piperacillin-tazobactam	4.5 g IV q 6 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Commonly used agent for empiric therapy in septic shock, has strong activity against Pseudomonas, Enterobacterales, anaerobes as well as gram positive bacteria such as MSSA, Streptococcus, and Enterococcus faecalis. Susceptible to degradation by AmpC and ESBL beta-lactamases.
Meropenem	1 g IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Commonly used agent in septic shock, has strong activity against Pseudomonas, Enterobacterales, anaerobes as well as gram positive bacteria such as MSSA and Streptococcus. Agent of choice in septic shock for patients at risk of ESBL-organisms. Increases risk of seizures.
Ceftolozane-tazobactam	cUTI/cIAI 1.5 g q 8 hr HABP/VABP 3 g q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Strong activity against Enterobacterales, carbapenem-resistant Pseudomonas, and EBSL+ organisms. Limited anaerobic activity so must combine with metronidazole for cIAI.
Ceftazidime-avibactam	2.5 g IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Strong activity against carbapenem resistant Pseudomonas, carbapenem-resistant Enterobacterales, and EBSL+ organisms. Limited anaerobic activity, so must combine with metronidazole for cIAI.
Cefiderocol	2 g IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Strong activity against carbapenem resistant Pseudomonas and carbapenem-resistant Enterobacterales. Combine with metronidazole for cIAI. Coverage for MBL producing organisms. Must add additional agent if concerned for gram positive organisms.

Table 1 (continued)

Antibiotic	Dosing	Clearance	Notes
Imipenem-cilastin relebactam	1.25 g IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Activity against carbapenem-resistant Enterobacterales. May restore activity against some carbapenem-resistant Pseudomonas. Has anaerobic activity.
Meropenem-vaborbactam	4 g IV q 8 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Strong activity against carbapenem resistant Enterobacterales. No additional activity against Pseudomonas compared to meropenem alone. Has anaerobic activity.
Aztreonam-avibactam	2.67 g loading dose followed by 2 g q 6 hr	Renally cleared with dose reductions necessary in patients with renal dysfunction and in patients on dialysis.	Strong activity against carbapenem resistant Enterobacterales. Coverage for MBL and other carbapenemase producing organisms (activity against all Ambler classes of beta-lactamases). Must add additional agent if concerned for gram positive organisms. No anaerobic coverage.

AUC, area under the curve; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; MSSA, methicillin-susceptible Staphylococcus aureus; g, grams; hr, hours; IV, intravenous; PO, oral administration; PK/PD, pharmacokinetic/pharmacodynamic; TDM, therapeutic drug monitoring; MAOI, monoamine oxidase inhibitor; CK, creatinine kinase; CNS, central nervous system; cUTI, complicated urinary tract infections; cIAI, complicated intraabdominal infection; HABP, hospital-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; ESBL, extended-spectrum beta-lactamases; MBL, metallo-β -lactamase; KPC, Klebsiella pneumoniae carbapenemase. For renally cleared antibiotics it is important to note that upward appropriate dosing of the antibiotic is necessary as renal function improves to avoid treatment failures

* The PK variability of beta-lactams is well studied and dose reductions according to renal function based on the manufacturers´ recommendations may cause inadequate plasma concentrations. Furthermore, augmented renal clearance may occur altering plasma drug levels. Individualized dose optimization by TDM is a potential solution here for the PK variability

The activity of all Gram Negative antibiotics is dependent on the underlying resistance mechanisms (OXA, MBL, KPC, etc.), which in turn are regionally variable

In conclusion, empiric antibiotic therapy in critically ill patients suspected of having sepsis remains a challenging decision. Patients with septic shock should promptly receive broad-spectrum antibiotics targeting likely bacteria such as MRSA and resistant GNB based on patient characteristics and local resistance rates. However, threshold rates for empiric antibiotic coverage of specific pathogen types are not currently supported by research. Nevertheless, at our institution for potentially life-threatening infections such as bacteremia and septic shock we recommend empiric coverage if the likely threshold rate is greater than ten percent. Another important issue influencing antibiotic selection and efficacy is source control which is beyond the scope of this review. Yet, we suggest that source control can be a decisive factor influencing patient outcomes with some infections (UTI, IAI, SSTI, etc.) and that clinicians need to always address this issue when dealing with infections in the CU setting. When patients present with severe sepsis, nearing septic shock, accelerated antibiotic administration may also be warranted. Overall, all infected patients likely benefit from antibiotic treatment regardless of the severity of presentation and harm arises when patients without infections receive antibiotics. Future AI/ML methods and rapid diagnostics that increase the pretest probability of infection and differentiate sepsis from mimics have the potential to greatly improve outcomes in all patients.

Pharmacokinetic considerations

Alterations of antimicrobial PK in critically ill patients, most notably, those with septic shock has been an area of research focus for over two decades. A bedside view of patients receiving lifesaving supportive therapies such as circulatory support via pharmacologic or mechanical means, mechanical ventilatory support, renal replacement therapies, and/or ECMO provide an outward reflection of in vivo variability of antimicrobial PK. When patient physiology returns to baseline functioning it is assumed that antimicrobial PK also normalizes. However, the fluctuations in antimicrobial absorption, distribution, metabolism, and elimination make dose optimization (Table 2) a challenge for the most experienced and resourced clinician despite recommendations to do so in clinical practice guidelines [13].

PK research in ICU patients has focused primarily on anti-pseudomonal beta-lactams and anti-MRSA agents, most often vancomycin. For beta-lactams, the PK/PD parameter associated with bacterial killing or efficacy is the time above organism MIC, but the target varies by infusion strategy and β-lactam class [52–54]. Preclinical data suggest β-lactam kill rate is maximized when serum concentrations exceed the MIC (T_{FREE} >MIC) for 40-70% of the dosing interval when administered by an intermittent infusion and 100% of the administration time or interval when given by prolonged infusion, defined as 3-4 hours or continuous infusions [54]. Despite this, the PK/PD goal most often studied is a serum concentration of four times the MIC at the end of the infusion interval (i.e., C_{min} or trough concentration). Not surprisingly, the percentage of antibiotic administrations achieving this target is consistently deemed to be insufficient in the early and subsequent treatment phases of sepsis when beta-lactams are administered via intermittent infusions [55, 56]. An important factor to be considered

Table 2 Antibiotic dose optimization

Drug or Drug Class	PK/PD Parameter (Target)	Patient factors influencing PK/PD	TDM
Beta-lactams	fT>MIC (Cmin >MIC)	Dose of IVFs administered during resuscitation phase, renal function	Within first 24-48 hours of initiation; with subsequent Bayesian estimation for dose adjustments.
Vancomycin	AUC/MIC (400-600)	Patient weight, renal function	Bayesian-estimated AUC within first 24-48 hours of initiation.
Aminoglycosides	AUC (70-100) or Cmax/MIC (8-10)	Patient weight, renal function	Extended Interval Dosing – Random level after the 1st dose. Traditional dosing – Cmax 1 hour after the start of the 3rd dose, Cmin immediately prior to 3rd dose.
Fluoroquinolones	AUC/MIC (80-125)	Renal function, Drug interactions with oral administration	Only recommended when treating mycobacterial diseases.

PK/PD = pharmacokinetic/pharmacodynamic TDM = therapeutic drug monitoring fT>MIC = free time greater than the minimum inhibitory concentration Cmin = minimum serum concentration AUC = area under curve Cmax = maximum serum concentration IVFs = intravenous fluids

when assessing PK/PD target attainment is the MIC used in the equation. When pathogen-specific MICs are not available, the default has been to utilize EUCAST MIC_{90} or equivalent. This "worst case scenario" approach for missing MIC data biases the results toward a lower likelihood of PK/PD target attainment. As expected, when beta-lactam PK/PD targets are derived from actual MICs compared to EUCAST clinical breakpoints, higher target attainment rates are observed [57, 58]. This suggests that fewer critically ill patients with Gram negative infections would be categorized as underdosed when MIC-derived targets are applied. Nevertheless, the value of prolonged antibiotic infusions most likely occurs with high MIC isolates identified locally emphasizing the importance of local MIC surveillance.

To optimize beta-lactam PK/PD target attainment, the use of prolonged infusions, have been recommended in critically ill patients by the Surviving Sepsis Campaign's International guidelines (weak recommendation, moderate quality of evidence) and a multi-society International Consensus Recommendations (conditional recommendation, very low certainty of evidence) [13, 59]. After the publication of these recommendations, two randomized controlled trials (MERCY (double-blind) and BLING III (open-label)) were reported, collectively enrolling over 7,600 patients. Both trials found no difference in Mortality between continuous infusion and intermittent infusions of beta-lactams at 28 and 90 days [60, 61]. Conversely, an individual patient data meta-analysis using a Bayesian Random-effects Model with vague priors, cumulated over 9000 patients from 17 randomized controlled trials (the MERCY and BLING III trials contributed 55% of study weight and 84% of the subjects) reported patients treated with prolonged infusions had a statistically significant reduction in 90-day mortality compared to intermittent infusions of beta-lactams [62]. Curiously, all prespecified subgroup analyses revealed no differences in 90-day mortality between infusion strategies, most notably in patients with septic shock (n = 5782 total patients), a population in which beta-lactam PK/PD target attainment could theoretically be improved with prolonged infusion. It is important to note that MERCY and BLING III may have been negative trials due to the lack of pathogens in the trial with very elevated MICs.

In addition to prolonged infusions, beta-lactam therapeutic drug monitoring (TDM) has been advocated to ensure trough concentrations (Cmin) are greater than the pathogen MIC (100% T_{Free} >MIC) [6]. It is recommended that the initial beta-lactam trough concentration should be measured 24-48 hours after the initiation of therapy, with incorporation of the result into dosing software to perform Bayesian estimation and regimen adjustment (if needed) followed by repeat TDM within 1-2 days. While TDM appears to improve beta-lactam PK/PD target attainment [63, 64], this has not translated to improved clinical outcomes in two recently published randomized controlled trials. The TARGET trial (n=249) found no difference in the primary outcome of mean SOFA score with and without TDM of piperacillin-tazobactam in patients with sepsis [65]. Likewise, secondary outcomes including 28-day mortality as well as ICU and hospital length of stay were not significantly improved in the TDM group. The DOLPHIN trial (n=388) paired beta-lactam TDM with Model-informed precision dosing optimization on days 1, 3, and 5 of therapy in ICU patients compared to standard dosing [66]. There were no significant differences in the primary outcome of ICU length of stay or any secondary outcomes including 28-day mortality.

Despite widespread implementation of prolonged beta-lactam infusions and promotion of TDM to optimize beta-lactam dosing in critically ill patients, results from the strongest quality of evidence don't support either strategy over standard dosing and clinical monitoring. Identifying patients at greatest risk of subtherapeutic beta-lactam concentrations, such as those with

augmented renal clearance and infecting organisms with high beta-lactam MICs should be the focus of clinical care and clinical trials moving forward [67, 68]. Additionally, TDM should be considered to avoid toxicities associated with certain antibiotic classes (glycopeptides, aminoglycosides).

Antibiotic de-escalation strategies and duration of treatment

ADE is the process of replacing broad-spectrum antibiotics with narrower-spectrum agents, discontinuing part of therapy (i.e., discontinuing agents for which there are no organisms isolated in culture or discontinuing one agent used as a part of combination therapy), or discontinuing all antibiotics if infection is no longer of concern [69]. Given the frequency of broad-spectrum antibiotic prescribing in the ICU, ADE is a core stewardship measure that should be routinely considered to prevent adverse drug events and mitigate the propagation of antimicrobial resistance, which is associated with over four million deaths annually and projected to increase by 70% by 2050 [70].

Several observational studies and small RCTs have demonstrated that ADE is safe in the critically ill [71–75]. The DIANA study, a prospective observational study of 152 ICUs in 28 countries, assessed the impact of ADE on mortality and clinical cure Rates in 1495 patients [71]. Although rates of ADE were low (16% of patients by day 3), 28 and 7-day mortality did not differ, and clinical cure rates were higher in patients who received ADE. Moreover, systematic reviews and meta-analyses have not found an increased incidence of adverse consequences associated with ADE and one demonstrated that ADE was associated with reduced mortality (RR 0.68, 95% CI 0.52-0.88) [76, 77].

In addition to the public health threats of AMR, antimicrobials may cause several adverse effects including nephrotoxicity, neurotoxicity, and hematologic toxicity, among others [78]. Furthermore, these agents may have destructive impacts on the gut microbiome that aids in eliminating potential pathogens [79]. Alterations to the microbiome from anti-anaerobic antibiotics have been demonstrated to worsen clinical outcomes. In a single-center retrospective study of over 3000 critically ill patients, the use of anti-anaerobic agents was associated with reduced survival (HR 1.14, 95% CI 1.02-1.28), VAP free days (HR 1.24, 95% CI 1.06-1.45), and infection-free days (HR 1.22, 95% CI 1.09-1.38) [80]. Additionally, the gut microbiome is a key defense against *Clostridiodes difficile* infections, which are associated with increased healthcare costs and hospital and ICU lengths of stay [81, 82]. By de-escalating antimicrobials promptly and appropriately, institutional costs and potential patient harm may be mitigated.

ADE should take place as soon as possible to minimize the potential adverse effects of broad-spectrum antibiotics [69, 77]. Current guidelines and consensus statements recommend daily assessment for ADE and de-escalating within 24 hours of definitive culture results. ADE can be performed by either the ICU treating clinicians or the antimicrobial stewardship team. Traditionally, ADE has only been possible after microbiologic cultures result, which take approximately 2 days for organism identification and 3 days for antimicrobial susceptibilities [83]. In recent years, tools such as RDTs have allowed for ADE significantly earlier. For example, antibiotic recommendations, including ADE, were provided just 5 hours after a multiplex bacterial PCR test was collected from bronchoalveolar lavage samples in the Flagship II trial [84]. Many types of RDTs are available such as multiplex PCRs, next generation sequencing, immunochromatography, MALDI-TOF, and enzyme immunoassay [85]. Many RDTs can detect specific bacterial species and resistance genes from direct specimens within hours. High negative predictive values of 92% to greater than 99% have been reported for various multiplex PCR tests [86–89]. Given the ability to quickly rule out organisms with RDTs, these data should be continually assessed along with routine culture results, to facilitate ADE as efficiently as possible. Other tools that can be used for ADE include urine antigen testing and nasal swabs for specific organisms of concern as well as multidisciplinary antimicrobial stewardship teams, CDS, and strategic language/reporting strategies of microbiologic results [90–93].

Figure 1 describes a proposed antimicrobial strategy for the ICU including ADE. When available, RDTs from the suspected site(s) of infection should be utilized for rapid ADE. For example, a patient with severe community-acquired pneumonia initiated on vancomycin and cefepime can be rapidly de-escalated based on a multiplex PCR detecting only *Haemophilus influenzae* from a tracheal aspirate. Since the hospital's antibiogram reports that 100% of *H. influenzae* isolates are susceptible to ceftriaxone and no other organisms were detected on the multiplex PCR, ceftriaxone monotherapy may be utilized even in the presence of patient risk factors for MRSA and *Pseudomonas*. Therapy may be even further de-escalated in the following days based on susceptibilities from the culture. Although it is more challenging to perform ADE in culture-negative infections, retrospective trials support the safety of ADE of broad-spectrum coverage, such as anti-MRSA agents, when cultures are negative [94, 95]. Before performing ADE, it is critical for ICU practitioners to consider the library of organisms the RDT detects as well as the clinical picture of the patient. Caution should be taken with ADE based on RDTs and cultures if concern exists for infection at other sites or if the patient is clinically worsening.

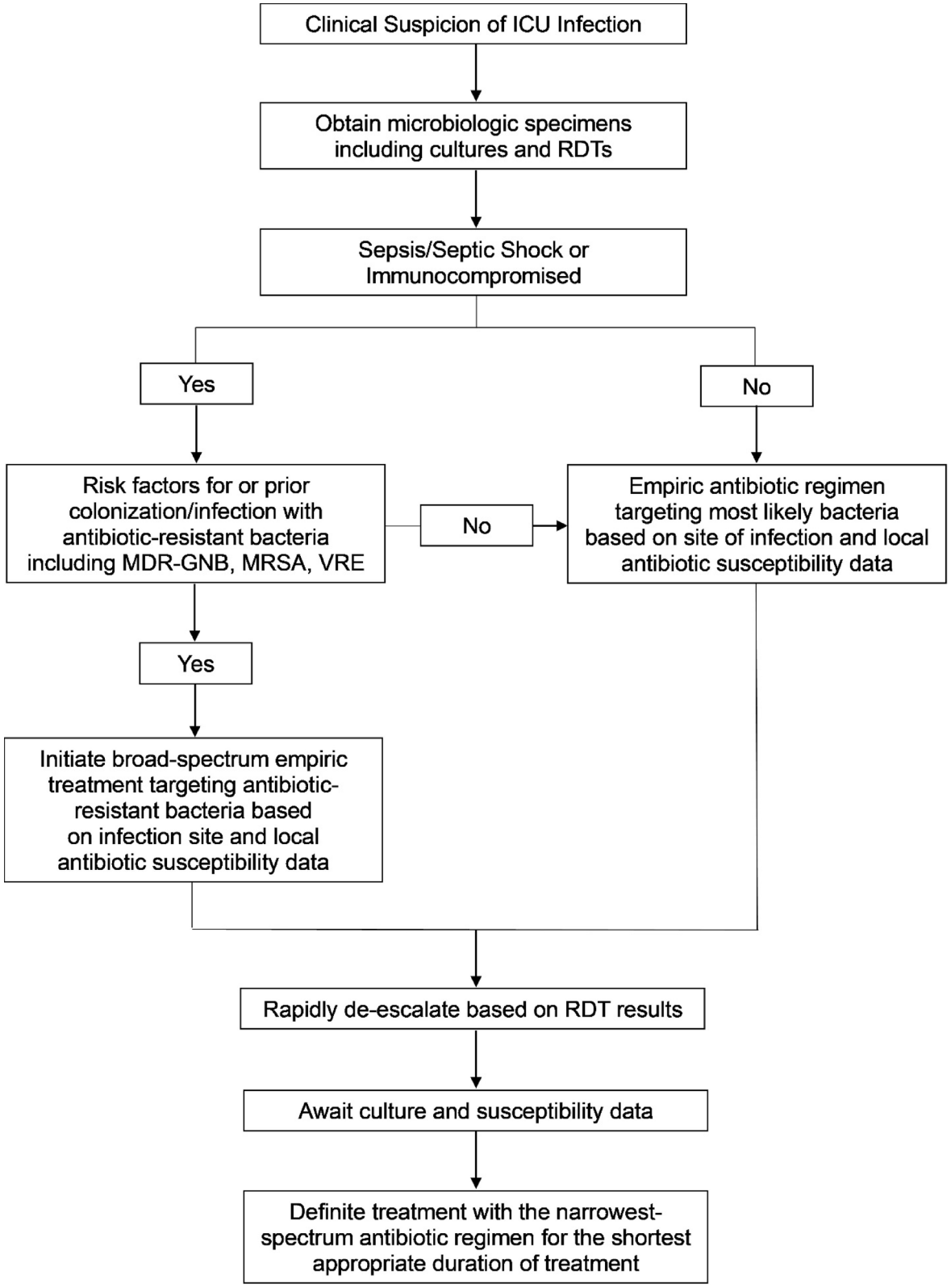
Clinical Suspicion of ICU Infection
Obtain microbiologic specimens including cultures and RDTs
Sepsis/Septic Shock or Immunocompromised
Yes
No
Risk factors for or prior colonization/infection with antibiotic-resistant bacteria including MDR-GNB, MRSA, VRE
No
Empiric antibiotic regimen targeting most likely bacteria based on site of infection and local antibiotic susceptibility data
Yes
Initiate broad-spectrum empiric treatment targeting antibiotic-resistant bacteria based on infection site and local antibiotic susceptibility data
Rapidly de-escalate based on RDT results
Await culture and susceptibility data
Definite treatment with the narrowest-spectrum antibiotic regimen for the shortest appropriate duration of treatment

Fig. 1 Algorithm for antimicrobial strategy in the ICU balancing appropriate initial antibiotic treatment with the need to minimize resistance emergence by employing stewardship practices. ICU, intensive care unit; RDTs, rapid diagnostic tests; MDR-GNB, multidrug resistant-Gram negative bacteria; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci

Treating infections with the shortest course of antimicrobials as clinically appropriate is another stewardship measure that can mitigate the risks associated with antibiotics. Multiple studies have confirmed that shorter durations of antimicrobials are as effective as longer durations for many types of infections [5, 96–101]. Table 3 describes recommended durations of therapy by site of infection [102–118]. These data combined with clinician assessment of clinical improvement/stability should be considered when deciding on the optimal antibiotic duration. This technique was employed in the recent REGARD-VAP Trial in which patients with VAP were randomized to individualized short-course treatment (≤7 days of therapy and as short as 3-5 days depending on defervescence, hemodynamic stability, and culture results) or usual care (≥8 days of therapy) [101]. The median durations of therapy were 6 days (IQR 5-7) and 14 days (IQR 10-21) in the individualized short-course and usual care groups, respectively. Individualized short courses of antibiotics were non-inferior to usual care and resulted in fewer adverse effects attributed to antimicrobials (risk difference −31%, 95% CI −37 to −25%). Shorter antibiotic courses have also been associated with reduced risk of developing antimicrobial resistance in observational studies, further demonstrating the importance of limiting antibiotic exposure [3, 119, 120]. While individualized care through clinical evaluation should be used as the primary means of determining duration of antibiotics, biomarkers such as procalcitonin may also aid clinicians in determining when to discontinue antibiotics and reduce antibiotic exposure [121, 122].

Table 3 Suggested duration of therapy by site of infection

Infection site	Suggested antibiotic duration
Pneumonia	≤5-7 days#
Community-acquired [102–104]	≤8 days*
Hospital-acquired, ventilator-acquired [105–107]	
Urinary tract infection	3-5 days
Uncomplicated UTI [108, 109]	5-7 days¶
Complicated UTI, pyelonephritis [110, 111]	
Intra-abdominal infection [96, 112, 113]	4-7 days¶
Skin and soft tissue infection [114–116]	5-7 days¶
Bloodstream infection [117, 118]	7-14 days†

UTI, urinary tract infection.

Antibiotic durations should always be individualized to the patient and their clinical status. Many studies have underrepresentation of critically ill patients.

#7 days is recommended in patients with community-acquired pneumonia caused by methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*.

*Consider prolonged courses of 14 days with non-fermenting gram-negative bacilli due to an increased risk of relapse/recurrence with shorter courses.

¶After definitive source control.

†Trials excluded immunocompromised patients, patients with indwelling prostheses, infectious syndromes that required prolonged durations, or organisms that required prolonged durations of treatment (i.e., *Staphylococcus aureus*, *Staphylococcus lugdunensis*). Most evidence for shorter courses is in bacteremia from gram negative bacteria secondary to urinary tract infections. Control of the primary source and blood culture clearance should also be achieved.

Antibiotics for infection prevention

One of the more prominent examples of antibiotic use to prevent nosocomial infection is SDD. Many ICU-acquired respiratory infections result from colonization of the upper and lower digestive tract with organisms typical of ICU-acquired infections. SDD involves the application of nonabsorbable antibiotics which are typically combined with an intravenous antibiotic, with the goal being to limit ICU-acquired infections by elimination of colonized microbes at the time of ICU admission [123, 124]. SDD has been widely adopted in some countries such as the Netherlands but has been slow to become widely accepted elsewhere [123, 125, 126]. One of the main reasons for hesitation in the use of SDD resides in concerns about increasing antimicrobial resistance by using antibiotics at the time of ICU admission, and whether use of SDD in areas with high antimicrobial resistance rates is feasible.

The SuDDICU trial in 2022 aimed to address these concerns, and was a cluster, Randomized, crossover trial of nearly 6000 mechanically ventilated patients across 19 ICUs in Australia. In this trial, ICUs were Randomly assigned to adopt an SDD strategy for alternating 12-month periods. 90-day Mortality was 27.0% in the group receiving SDD, compared to 29.1% of those receiving standard of care, which did not meet statistical significance [124]. A large systematic review and meta-analysis was also published in 2022 examining the effect of SDD in mechanically ventilated patients. This study included 32 Randomized trials with nearly 25,000 patients and found that the relative risk for Mortality with SDD was 0.91, suggesting a mortality benefit for the use of SDD in critically ill adults receiving mechanical ventilation [127]. However, questions remain regarding the use of SDD in ICUs with higher Rates of antimicrobial resistance. An RCT in 2018 looked at the effects of chlorhexidine, selective oral decontamination, and SDD on the subsequent development of blood stream infections in ICUs with higher rates of infections with ESBL−producing Enterobacterales, and found that the use of SDD was not associated with lower rates of bloodstream infections by MDR-GNB [128]. SDD therefore remains popular and in high use in certain countries with lower rates of MDR organisms but has not been adopted by ICUs in the US due to concerns for lack of efficacy and concerns regarding worsening antimicrobial resistance.

The use of inhaled antibiotics to prevent nosocomial pneumonia, particularly VAP is another area of active research. A single center RCT in 2014 investigated nebulized colistin in patients who had been mechanically

ventilated for longer than 48 hours and found that 30-day VAP rates did not differ significantly in the nebulized colistin group (16.7%) and the standard of care group (29.8%) [129]. A large RCT compared the use of a 3-day course of inhaled amikacin compared to standard of care in critically ill adults receiving mechanical ventilation for over 72 hours [130]. This was a multicenter trial that enrolled 850 patients and found that 28-day VAP Rates were 15% in the amikacin group compared to 22% in the control group [130]. It is important to note that the definition of VAP used in this trial included a positive culture from a respiratory sample, and it is therefore possible that the incidence of VAP could be underestimated in the group that received inhaled amikacin as a consequence of antibiotic exposure, Rather than lower Rates of true VAP. Further evidence for the use of prophylactic inhaled antibiotics was seen in a systematic review and network meta-analysis, which included seven RCTs, with 1445 patients [131]. This study found that prophylactic antibiotics were associated with lower rates of VAP, and found particular benefit for inhaled aminoglycosides, but also found no difference in mortality, ICU length of stay, or duration of mechanical ventilation [131]. Further studies of nebulized antibiotics to prevent VAP are needed, given the lack of improvement in patient related outcomes. The decrease in rates of VAP seen in RCTs may be more representative of decreased microbiological diagnoses in the presence of antibiotic use.

The use of antibiotics to prevent infection has been investigated in patients with acute brain injury. The PROPHY-VAP trial investigated the use of a single dose of intravenous ceftriaxone in adult patients undergoing mechanical ventilation with a GCS of ≤ 12 [132]. The etiologies for brain injury in this trial were brain trauma, subarachnoid hemorrhage, and hemorrhagic or ischemic strokes. Incidence of VAP was 14% in the ceftriaxone group compared to 32% in the control group, which was associated with a statistically significant hazard Ratio of 0.60. Like the inhaled antibiotic trials, the definition of VAP in this study necessitated a positive culture, and thus the use of ceftriaxone may have influenced the ability to grow bacteria on culture and may underestimate true rates of VAP. This study did show improvements in ICU-free days, hospital free days, and there was a trend towards improvement in mortality [132]. Clinicians should balance the potential benefits of prophylactic antibiotic use in the ICU versus potential adverse effects including resistance emergence.

Recent studies also suggest that prophylactic antibiotics used in the ICU were inappropriate up to 50% of the time and this was more likely to occur in surgical ICUs, mixed surgical ICUs, mixed medical ICUs, and mixed cardiac ICUs [133, 134]. Moreover, inappropriate prophylactic antibiotics were often used more than two-fold longer in duration than nonprophylactic regimens [133]. The use of such inappropriate prophylactic antibiotic regimens may represent an important area for stewardship interventions in the ICU.

Table 4 Potential antmicrobial stewardship practices for the icu*

1. Avoidance of Unnecessary Antibiotics
a. Routine structured antibiotic review by pharmacists/microbiologists [138, 139]
b. Use of microbiologic rapid diagnostic tests to direct antibiotic treatment [143, 144]
c. Antibiotic timeouts and automatic antibiotic stop orders [141, 142]
d. Computerized antibiotic decision support guidance [151, 152]
2. Antibiotic De-escalation
a. Use of microbiologic rapid diagnostic tests to narrow antibiotic spectrum [143, 144]
b. Traditional microbiologic cultures and antibiotic susceptibilities for definitive antibiotic selection [138]
c. Automated prescriber feedback/computerized decision support [151, 152]
d. Routine structured antibiotic review by pharmacist/microbiologist [138, 139]
3. Employ Shortest Effective Antibiotic Regimen
a. Use of national/international guideline recommended antibiotic durations [96, 101, 138]
b. Optimize antibiotic pharmacokinetic/pharmacodynamic properties [62]
c. Biomarkers to guide antibiotic stoppage and shorten treatment courses [145, 147]
d. Routine structured antibiotic review by pharmacist/microbiologist [138, 139]
e. Computerized antibiotic decision support guidance [151, 152]

*Supporting references are provided as listed in the text

Stewardship considerations

AS involves a comprehensive methodology striving to improve patient outcomes, combat the emergence of resistance, and control costs by improving antimicrobial use [135]. AS is a commonsense approach to antibiotic use that should be implemented in some manner within all ICUs [135, 136]. From a practical standpoint, AS aims to reduce unnecessary antibiotic exposure in the ICU, especially those agents with a broad-spectrum of activity. This overreaching aim is supported by evidence suggesting that longer courses of antibiotic exposure can quantitatively be linked to greater resistance emergence without a ceiling effect [3, 137]. Table 4 provides an overview of stewardship practices that have been successfully implemented within ICUs that can be incorporated in locally developed AS programs. Foremost amongst these practices are reserving antibiotics for patients with bacterial infections likely to benefit from their use, de-escalating to the narrowest antibiotic regimen with intrinsic activity against the identified pathogens, and employing the

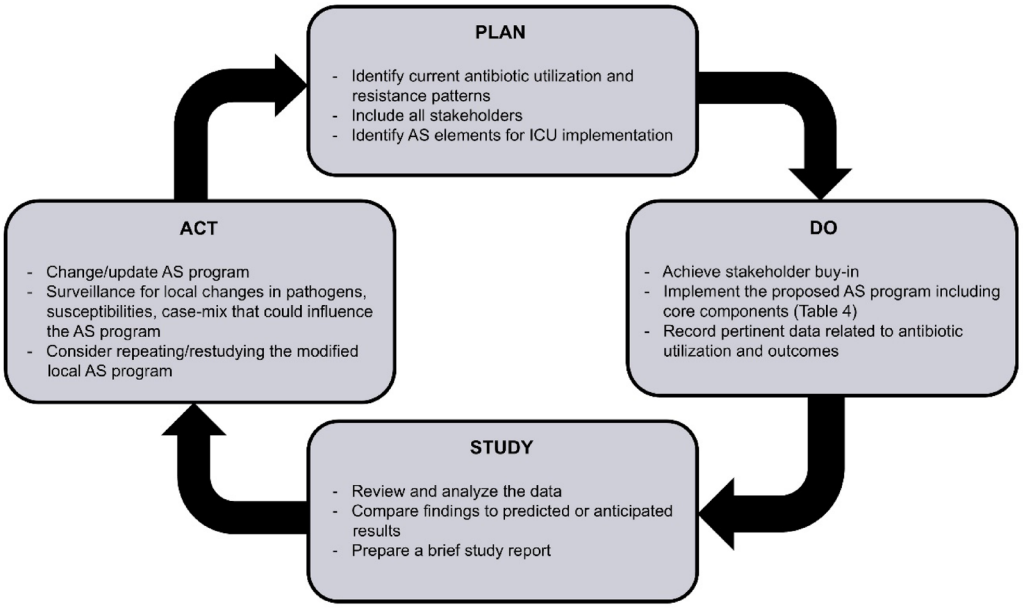
PLAN
- Identify current antibiotic utilization and resistance patterns
- Include all stakeholders
- Identify AS elements for ICU implementation
DO
- Achieve stakeholder buy-in
- Implement the proposed AS program including core components (Table 4)
- Record pertinent data related to antibiotic utilization and outcomes
STUDY
- Review and analyze the data
- Compare findings to predicted or anticipated results
- Prepare a brief study report
ACT
- Change/update AS program
- Surveillance for local changes in pathogens, susceptibilities, case-mix that could influence the AS program
- Consider repeating/restudying the modified local AS program

Fig. 2 A quality improvement implementation strategy for introducing and evaluating stewardship practices in the ICU. AS, antimicrobial stewardship; ICU, intensive care unit

shortest course of effective antibiotic treatment for the infected patient.

Effective AS programs rely on buy-in by all ICU stakeholders regarding their clinical importance and necessary successful implementation. The use of antibiotic review practices to eliminate unnecessary antibiotic use, especially broad-spectrum agents, as well as reduce treatment durations is well described. Such review practices have employed designated stewards including pharmacists and microbiologists, while others have utilized prescriber education strategies and antibiotic timeouts or predetermined stop orders [138–142]. Microbiologic RDTs implemented as part of an AS program have also been used to exclude the presence of bacterial infections while allowing for the identification of non-bacterial targets [84, 143, 144]. Implementation of RDTs within an AS program has been associated with reduced hospital mortality in patients with bloodstream infections [143] and greater overall appropriate antibiotic use to include de-escalation [84]. Similarly, biomarkers such as procalcitonin have reduced the duration of empiric antibiotics within ICUs and have been associated with reduced patient mortality [145–147].

Antibiotic de-escalation based on the results of RDTs and conventional microbiology culture and susceptibilities is a well-accepted, yet inconsistently applied practice [148]. Antibiotic de-escalation has been associated with significant reduction in the subsequent emergence of resistant bacterial infections without any demonstrable harm [149, 150]. The unrecognized ill effects of antibiotics on patient and environmental outcomes have been proposed as a reason for the lack of routine uptake of de-escalation practices [140, 148]. A systematic review of antibiotic de-escalation was able to identify factors associated with its successful implementation and demonstrated that the pooled effect of antibiotic de-escalation on mortality was protective (relative risk, 0.68; 95% confidence interval, 0.52-0.88) [76]. Antibiotic de-escalation should be a routine measure employed in all AS programs within ICUs [148, 149].

CDS utilizing automated medical records represents a potential solution for improving antimicrobial prescribing practices and containing antimicrobial resistance by enhancing clinical decision making [151]. Most successful attempts at CDS have been employed outside of the ICU setting [152]. The hope is that with improvements in computational abilities and refined algorithms, the success of CDS can be extended into ICUs as well [153]. Unfortunately, not all resource intensive AS programs applied in the ICU have been successful [154]. For this reason it is important to develop and implement individualized AS programs customized to match unit-specific populations, resource availability, workflow, and local culture [135, 136, 155]. Utilizing the recently developed CDC tool for assessing antibiotic appropriateness in the inpatient setting may help to develop individualized AS programs [156]. Antibiotic stewardship programs must ensure that improving overall antibiotic use, not simply reducing antibiotic acquisition costs or increasing de-escalation alone, is the primary focus. Increasing awareness of the importance of AS in the ICU, greater availability of artificial intelligence support of clinical decision making, and more limited availability of new antimicrobial agents should drive routine acceptance and

implementation of AS programs in the ICU as a quality improvement initiative (Fig. 2) [153, 157].

Conclusions

Antibiotics are among the most commonly prescribed drugs in the ICU having effects on the treated patient as well as on future patients due to resistance emergence. Strategies aimed at optimizing the use of antibiotics in the ICU should routinely be employed and supported by ICU practitioners. Multifaceted strategies using antibiotic optimization practices noted above will be the most likely to optimize patient outcomes while safeguarding antibiotics for the long-term by minimizing resistance emergence.

Abbreviations

ADE	Antibiotic de-escalation
ARO	Antibiotic-resistant organism
AMR	Antimicrobial resistance
AS	Antimicrobial stewardship
CDC	Centers for Disease Control and Prevention
CDS	Computerized decision support
CMS	Centers for Medicare and Medicaid Services
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
EPIC III	European Prevalence of Infection in Intensive Care
ESBL	Extended-spectrum beta-lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GCS	Glasgow Come Scale
GNB	Gram negative bacteria
IAI	Intraabdominal infection
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
MALDI-TOF	Matrix-associated laser desorption/ionization time-of-flight
MBL	Metallo-β-lactam
MDR-GNB	Multidrug resistant-Gram negative bacteria
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
PCR	Polymerase chain reaction
PK/PD	Pharmacokinetic/pharmacodynamic
RCT	Randomized controlled trial
RDTs	Rapid diagnostic tests
SDD	Selective decontamination of the digestive tract
SSTI	Skin and skin structure infection
TDM	Therapeutic drug monitoring
US	United States
UT	Urinary tract infecton
VAP	Ventilator-associated pneumonia
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

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Competing interests

The authors declare no competing interests.

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